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Synthesis of 2-Aminophosphates via S_N2-Type Ring Openings of Aziridines with Organophosphoric Acids

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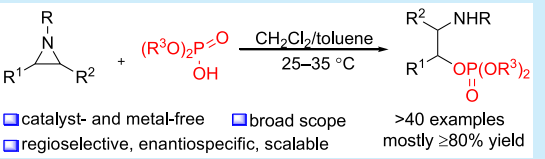
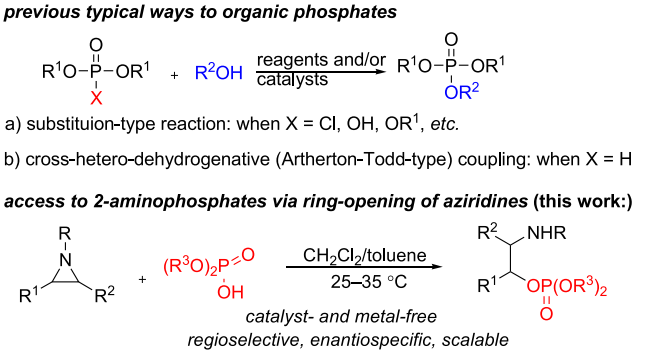
Supporting Information

ABSTRACT: The synthesis of 2-aminophosphates is achieved by a S_N2-type ring opening reaction of various *N*-protected or free aziridines with phosphoric acids in a regiospecific and/or enantiospecific way. A one-pot, two-step procedure is also developed enabling direct access to 2-aminophosphates from olefins without isolation of the aziridine intermediates.



Organic phosphates are a very important structural motif present in numerous biologically active compounds, such as glycolipids and nucleic acids. In pharmaceutical studies, the introduction of a phosphate moiety has been found to lead to enhanced solubility and, thus, could regulate the distribution and bioavailability of the parent drug/prodrug molecules.[1] They are also useful leaving groups for cross-coupling and nucleophilic substitution reactions.[2] The most common way to organic phosphates rely on the reaction between a phosphoryl halide or a phosphoric acid and an alcohol,[3] while methods including the Artherton−Todd-type cross-heterodehydrogenative coupling reaction,[4] the phosphoryloxylation of alkenes and alkynes,[5] and others[6] have also been developed (see Scheme 1). Metal catalysts and/or stoichiometric amount of base additives are usually required in these methods.

Scheme 1. Synthetic Approaches to Organic Phosphates



Aziridines belong to a class of readily available synthons bearing rich reactivity mainly derived from its unique strained three-membered ring system. The ring opening reaction of aziridines with nucleophiles has served as an efficient approach to a variety of nitrogen-containing compounds, although examples with *N*-unprotected free aziridines are very rare.[7] Moreover, despite the successful incorporation of several oxygen-nucleophiles, including aldehydes and ketone carbonyls,[8] alcohols and phenols,[9] and carboxylic acids[10] in this reaction under either Lewis or Brønsted acid catalysis, the ring opening of aziridines with organic phosphoric acid, which could provide a straightforward way to 2-aminophosphates, has been rarely studied.[11] Notably, chiral BINOL-derived phosphoric acids have been showed by List and co-workers as efficient catalyst in effecting highly enantioselective ring opening of aliphatic *N*-acylaziridines with carboxylic acids, and the authors observed the degradation of the catalyst and ascribed this to the direct addition of the catalyst to the aziridine.[10] On the other hand, the 2-aminophosphate structure is an integral component in many pharmaceutically relevant molecules (Figure 1). For example, fosamprenavir is a drug used for the treatment of HIV-1 infections;[12] FTY 720-P is a phosphorylated active metabolite of fingolimod (FTY 720), a $S1P_1$ agonist immunomodulator;[13] and two duocarmycins analogues demonstrated substantial hypoxia-selective anticancer activity.[14] Therefore, the development of a general

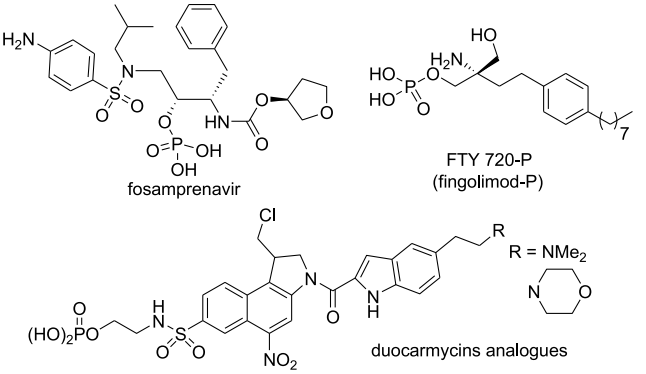


Figure 1. Representative bioactive molecules bearing the 2-aminophosphate motif.

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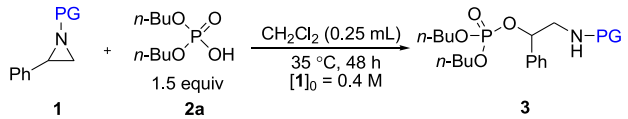
and mild synthetic way to form 2-aminophosphates should be highly desirable.

As part of our continued interest in exploring the synthetic utility potential of aziridines,[15] we describe herein a catalyst and metal-free way to 2-aminophosphates via direct ring opening of aziridines with organic phosphoric acids. The reaction features also a broad substrate scope, tolerating *N*-protected/unprotected aryl- and alkyl-substituted aziridines and could proceed in a highly enantiospecific way.

Our study commenced with the examination of a series of styrene-derived aziridines bearing different *N*-protecting groups (PGs), which showed a generally good scope in this respect (see Table 1). Aziridines **1a**–**1d** with different

Table 1. Scope of Aziridines with Respect to *N*-Protecting Group (PG)



1 **2a** **3**

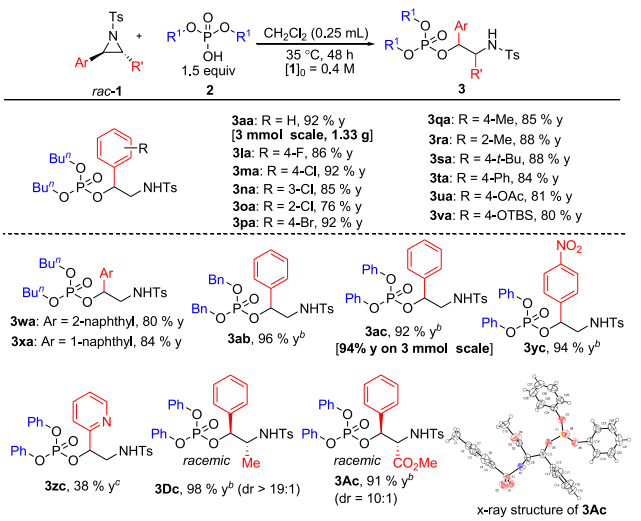
entry	1 (PG)	3	yield[a] (%)
1	**1a** (Ts)	**3aa**	89
2	**1b** ($PhSO_2$)	**3ba**	85
3	**1c** (Ns)	**3ca**	82
4	**1d** ($mesitylSO_2$)	**3da**	83
5	**1e** (Bus)	**3ea**	86
6	**1f** (Boc)	**3fa**	78
7	**1g** (Cbz)	**3ga**	81
8	**1h** (2-nitrobenzoyl)	**3ha**	64
9[b]	**1i** (4-anisyl)	**3ia**	-
10	**1j** (Bn)	**3ja**	71
11	**1k** (H)	**3ka**	65
12	**1C** (Ac)	**3Ca**	63

[a]Yields of isolated products. [b]A complicated system was observed both by TLC and by ^1H NMR analysis.

arylsulfonyl groups were well tolerated in the reaction, while the presence of an electron-donating group on the benzene ring seems to be slightly favored, in terms of yield (see Table 1, entries 1–4). Notably, although dried CH_2Cl_2 has been generally used in this study, an experiment in commercial CH_2Cl_2 using **1a** under the otherwise same reaction conditions provided equally high yield (see Table S1 in the Supporting Information for solvent screen with aziridine **1a**). In addition, the addition of 1.5 equiv of K_2CO_3 to the reaction system of entry 1 in Table 1 completely inhibited the reaction, suggesting that the phosphoric acid may also serve as a catalyst/promoter for the ring opening. The aliphatic *t*-butylsulfonyl group (Bus), which has been introduced by Sharpless and co-workers and has been shown to be easily removable under acidic conditions,[16] was also well-suited in this reaction (see Table 1, entry 5). Moreover, aziridines bearing other common protecting groups, such as Boc and Cbz, also underwent the reaction uneventfully, albeit with somewhat reduced yields (see Table 1, entries 6–8). However, the reaction of *N*-aryl aziridine **1i** gave a very complicated system (Table 1, entry 9). We presumed that it is due to the high reactivity of the aniline moiety in the resultant product **3ia** as *N*-nucleophile to further react with the aziridine **1i**, despite the presence of an excess of the phosphoric acid **2a**.[17] Notably, the *N*-benzylaziridine **1j** and the free aziridine **1k**, which are usually considered to be unactivated aziridines and are less popular as electroplies in ring opening reactions, were also tolerated in the reaction (Table 1, entries 11 and 12). The product **3ka** bearing a free amino group should be more favorable for further synthetic manipulations.

Subsequently, the reaction scope with respect to 2-aryl-substituted *N*-tosylaziridines was then probed with di-*n*-butylphosphate **2a** (see Scheme 2). Generally, the reaction

Scheme 2. Scope of Aryl-Substituted Aziridines[a]



[a]Yields of isolated products are reported. [b]Run at 25 °C for 10 h. [c]Run at 35 °C for 72 h.

worked well with a range of styrenyl aziridines bearing various electron-withdrawing or electron-donating substituents on the benzene ring and two naphthyl aziridines, providing the desired products **3aa**–**3xa** in high yields. Compared to **2a**, the more-acidic dibenzyl phosphate **2b** and diphenyl phosphate **2c** demonstrated higher reactivity in this reaction to provide the desired products **3ab**–**3yc** in excellent yields within remarkable reduced reaction times at room temperature. The heterocyclic 2-pyridyl aziridine was also tolerated in the reaction to deliver the product **3zc**, albeit with a low yield, which was due to an incomplete conversion of the aziridine, and increasing the amount of phosphoric acid **2c** to 4.0 equiv led to no apparent improvement. Notably, 2,3-disubstituted-*N*-tosyl aziridines derived from internal alkenes such as *trans*-*β*-methylstyrene and methyl cinnamate were also well-tolerated in this reaction to provide the corresponding products **3Dc** and **3Ac** in high yields and excellent diastereoselectivity; the relative configuration of the major diastereomer product **3Ac** was unambiguously assigned by X-ray crystallographic analysis (CCDC No. 1888926).

Next, a range of alkyl-substituted aziridines were also examined in the reaction (Scheme 3). The reactivities of such aziridines are generally lower, compared to those of aryl-substituted ones, and thus the more-reactive diphenylphosphate **2c** were used for the examination. By comparison, the reaction using phosphate **2a** required a much longer reaction time at a higher temperature to provide the corresponding product **5ba** in comparably high yield. For cyclic *meso* aziridines, the reactivity diminished as the size of the ring increases, and a similar trend has been observed in previous related studies.[15b] The acyclic *meso* aziridine is also well-tolerated in the reaction to provide the product **5fc** in excellent

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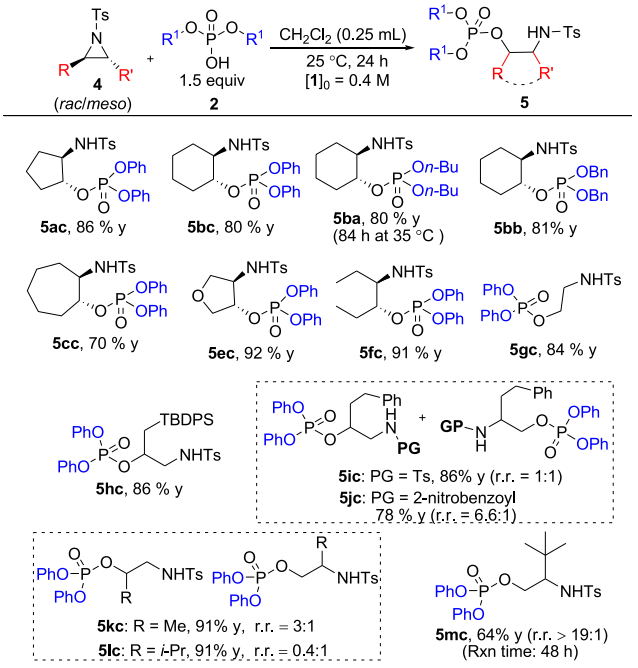
Scheme 3. Scope of Alkyl-Substituted Aziridines[a]

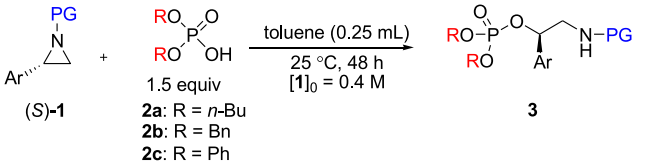


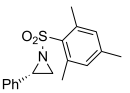
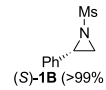
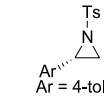
[a]Yields of isolated products are reported. The regioisomeric ratios (rr) were determined by ^{1}H NMR analysis.

yield. For racemic 2-alkylaziridines, the 2-silylmethylaziridine provided the desired product **5hc** as a single regioisomer in high yield, because of the presence of *β*-silicon effect.[18] In the absence of this effect, very poor regioselectivities were observed (**5ic**, **5kc** and **5lc**), while the two regioisomeric products were isolated in a high yield as inseparable mixtures by silica gel chromatography. Notably, while the use of other phosphoric acids including **2a** and **2b** led to no improvement in the regioselectivity, changing the *N*-protecting group of the aziridine from the Ts group to the 2-nitrobenzoyl group, the regioselectivity could be significantly improved to 6.6:1 (**5jc**) with the regioisomer resulting from the attack at the 2-substituted carbon being the major product, albeit with a somewhat decreased yield. For the aziridine **4m** bearing a bulky *t*-butyl group at the 2-position, the product **5mc** resulting from the attack at the sterically favored terminal carbon of the aziridine was isolated as the solo product (see the Supporting Information for details on structural assignment based on NMR analyses).

We then turned our attention to the synthesis of nonracemic 2-aminophosphates via the enantiospecific ring-opening of enantioenriched aziridines (Table 2). Multiple factors including the structures of the phosphoric acids, solvent, and structures of the aziridine (*N*-protecting groups PG and the Ar group) were found to be influential on the enantiospecificity (es) of the reaction. The enantiospecificity decreased as the acidity of the phosphoric acid **2** increased (Table 2, entries 1−3). Performing the reaction in the more polar CH_2Cl_2 led to a significant decrease in the enantiospecificity value (Table 2, entry 4). For other sulfonyl groups examined, a bulky mesityl group is favored over a simple methyl group, in terms of enantiospecificity (see Table 2, entries 5 and 6). The *N*-Cbz aziridine provided results comparable to those obtained with the *N*-Ts aziridine (Table 2, entry 7). For the Ar group, the presence of an electron-withdrawing group (Cl) is clearly more

Table 2. Studies on the Enantiospecific Ring Opening of Enantioenriched Aziridine



entry	1	2	3 (yield %)[a]	ee %[b] (es %)
1	 (S)-1a (>99% ee)	2a	(*R*)-3aa (81)	93 (93)
2		2b	(*R*)-3ab (92)	91 (91)
3		2c	(*R*)-3ac (90)	82 (82)
4[c]		2c	(*R*)-3ac (91)	73 (73)
5	 (S)-1d (99% ee)	2a	(*R*)-3da (72)	96 (97)
6	 (S)-1B (>99% ee)	2a	(*R*)-3Ba (81)	84 (84)
7	 (S)-1g (99% ee)	2a	(*R*)-3ga (80)	94 (94)
8	 Ar = 4-ClC6H4 (S)-1m (98% ee)	2a	(*R*)-3ma (82)	96 (98)
9	 Ar = 4-tolyl (S)-1q (97% ee)	2a	(*R*)-3qa (78)	79 (82)

[a]Yields of isolated products. [b]Determined by chiral HPLC. [c]Performed in CH_2Cl_2.

favored than an electron-donating group (Me), in terms of both yield and enantiospecificity (Table 2, entries 8 and 9). These results correlate well with findings in previous related studies on Lewis acid-catalyzed nucleophilic ring openings of aziridines, which thus suggests that the current reaction may also proceed via a S_N2-type mechanism, as originally proposed by Ghorai and co-workers.[8b]

Next, in light of the simplicity of the above ring opening reaction system, we then wondered if a tandem procedure enabling direct access to 2-aminophosphates from alkenes without the need for the isolation of the aziridine intermediates could be developed. After some experimentation, a two-step sequence involving the Cu(II)-catalyzed aziridination,[19] followed by the ring-opening reaction in a one-pot fashion, was established. As illustrated in Scheme 4, this new one-pot procedure worked well with both aromatic and aliphatic alkenes to provide the desired 2-aminophosphate products in good yields.

To illustrate the potential synthetic utility of this reaction, some of the products were then transformed to other useful structures (Scheme 5). The reduction of the enantioenriched product **3aa** by $LiAlH_4$ in tetrahydrofuran (THF) provided chiral 2-aminoalcohol **6** in 85% yield, with little loss in the enantiopurity. The absolute configuration of **6** was determined

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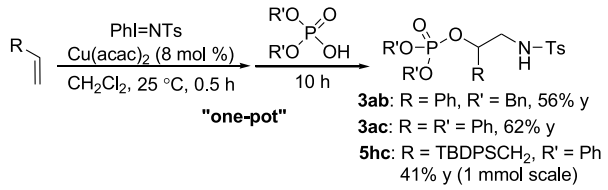
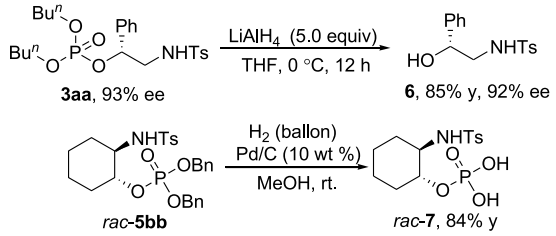
Scheme 4. One-Pot Aminophosphoryloxylation of Alkenes



Scheme 5. Synthetic Transformations of Products



by comparison of the specific rotation value with that of literature data (see the Supporting Information for details). In addition, the product **5bb** could be transformed to 2-aminophosphoric acid **7** in high yield via routine hydrogenation.

In summary, we disclose that the regioselective and enantiospecific ring opening of aziridines with organic phosphoric acids could be performed in a catalyst-free way under mild reaction conditions. Such a reaction has a broad scope in that it applies to both aryl- and alkyl-substituted aziridines bearing various *N*-protecting groups, including *N*-unprotected free aziridine, providing ready access to a variety of potentially useful 2-aminophosphates. A one-pot two-step procedure for accessing 2-aminophosphates from olefins, phosphoric acids, and (*N*-(tosylimino))phenyliodinane is also developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01302.

Experimental procedures, ^{1}H, ^{13}C, ^{31}P NMR copies for all new compounds, and HPLC traces (PDF)

Primary NMR files for all new compounds (ZIP)

Accession Codes

CCDC 1888926 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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